IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF SOUTH CAROLINA
CHARLESTON DIVISION

IN RE: LIPITOR (ATORVASTATIN CALCIUM) MARKETING, SALES PRACTICES AND PRODUCTS LIABILITY LITIGATION	MDL NO. 2:14-MN-2502-RMG ORAL ARGUMENT REQUESTED
This document relates to: All Cases	

PLAINTIFFS' RESPONSE TO MOTION TO EXCLUDE THE TESTIMONY OF PLAINTIFFS' REGULATORY EXPERT DR. FLEMING

H. Blair Hahn (Fed. I.D. # 5717)
RICHARDSON PATRICK WESTBROOK & BRICKMAN, LLC
1037 Chuck Dawley Blvd., Bldg. A
Mount Pleasant, SC 29464
Telephone: (843) 727-6500
Facsimile: (843) 727-6642
bhahn@rpwb.com

Plaintiffs' Lead Counsel

Ramon Rossi Lopez (CA 86361)
LOPEZ MCHUGH, LLP
100 Bayview Circle, Suite 5600
Newport Beach, CA 92660
Telephone: (949) 737-1501
Facsimile: (949) 737-1504
rlopez@lopezmchugh.com

Jayne Conroy (NY 8611)
David F. Miceli (GA 503900)
SIMMONS HANLY CONROY
One Court St.
Alton, IL 62002
Telephone: (618) 259-2222
Facsimile: (843) 7276642
jconroy@simmonsfirm.com
dmiceli@simmonsfirm.com

Plaintiffs' Executive Committee on Behalf of the Plaintiffs' Steering Committee

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INTRODUCTION

Defendant Pfizer, Inc. ("Pfizer") seeks to exclude the opinions of Plaintiffs' expert, G. Alexander Fleming, M.D., on a grab-bag of grounds.[1] Unable to find one significant flaw in Dr. Fleming's opinions or credentials, Pfizer tries a scattershot approach, apparently on the theory that if it shoots enough pellets at Dr. Fleming's opinions, one of them will hit the mark. But none do. Dr. Fleming provides narrow opinions that are within his area of expertise, the regulatory program at the federal Food and Drug Administration ("FDA"). He properly relies on his training and experience, the opinions of other notable experts in related fields, and the evidence in this case to form his own opinions. His opinions are, moreover, fully supported. Dr. Fleming's opinions are proper under Federal Rules of Evidence 104(a), 401, 402, 403, 702, and 703, and should not be excluded.

BACKGROUND

Dr. Fleming is a medical doctor, board-certified in Internal Medicine and Endocrinology. He was a Medical Officer and Supervisory Medical Officer at the FDA for 12 years, from 1986-1998. There, he was responsible for the regulation of diabetes and other metabolic drugs. As head of the clinical reviewers of endocrine and metabolic treatments at FDA (which includes drugs for diabetes treatment), he approved the first statins, growth hormones, and all diabetes drugs in the 1990s up to the time he retired from FDA. All of those approvals included approval of the labeling. He was also responsible for review, revision, approval or denial of proposed label changes for all drugs in the Metabolic Group. His duties at FDA also included representing the agency at international initiatives such as the International Conference on Harmonisation (ICH), where he was a member of three working groups. The ICH seeks to harmonize drug regulatory efforts on a global basis. He was stationed as the FDA representative at the World Health Organization (WHO)

[1] Pfizer also sweeps Dr. Fleming into its motion to exclude expert opinions that Lipitor has not been shown to be effective for primary prevention in women, even though Dr. Fleming does not offer that opinion. *See* Plaintiffs' Steering Committee Memorandum of Law in Response to Pfizer, Inc.'s Motion to Exclude Expert Testimony and Claims that Lipitor Is Not Effective for and Should Not Be Approved for Primary Prevention in Women.

in Geneva from 1992 to 1993 and served as Chair of the Professional Education and Training programs for the FDA's Center for Drug Development and Research (CDER), and co-founded and served as Editor-in-Chief of CDER's Virtual Journal of Drug Evaluation. He was also a major contributor to the FDA's Good Review Practice (GRP) initiative, which sought to establish principles, standards, and practices for the review of drug safety and effectiveness. Pfizer Ex. 2 at 1-2.

Dr. Fleming has published in medical and scientific journals on the subjects of diabetes treatment and federal regulation of food, drugs, and medical devices, and has written several book chapters on similar topics. The most recent chapter, "Regulatory Considerations for Early Clinical Development," is included in *Translational Research Methods for Diabetes, Obesity and Cardiometabolic Drug Development*, to be published by Springer in January 2015. He is the author of *Optimizing Therapeutic Development in Diabetes*, published in 2000. *Id.* at 2.

Dr. Fleming has consulted for a number of pharmaceutical companies, including Pfizer. Pfizer E.x 2 at 3.

Dr. Fleming's report contains four opinions: (1) the manufacturer of a drug, not the FDA, holds primary responsibility for ensuring that its drug label fully and accurately discloses the risks and benefits of its drug; (2) Based on the clinical trial data submitted with the NDA, Pfizer should have warned about glycemic abnormalities and should have undertaken additional testing with respect to Lipitor and hyperglycemia and diabetes; (3) Pfizer had a duty to inform the FDA about a Japanese label update in June 2003 that concerned hyperglycemia; and (4) the data from Pfizer's ASCOT study did not establish the efficacy of Lipitor in women for primary prevention.[2] As he is required to do under Fed. R. Civ. P. 26, Dr. Fleming's report also contains the bases and reasons for his opinion, including background information about statins and diabetes, the regulatory history

[2] Although Pfizer seeks, in this motion, to exclude all four of Dr. Fleming's opinions, and makes arguments regarding each of them, the fourth opinion, concerning the ASCOT trial and the efficacy of Lipitor for primary prevention in women is also the subject of Pfizer's separate motion to preclude testimony that such efficacy has not been shown. Thus, Pfizer has filed two separate motions to exclude this same opinion.

of Lipitor, FDA regulatory practices, and specific matters underlying the formation of each of his four opinions.

LEGAL STANDARDS

Under *Daubert*, an expert may provide opinions under Federal Rule of Evidence 702 that are reliable, and "assist the trier of fact to understand the evidence or to determine a fact in issue." *Daubert v. Merrell Dow Pharmaceuticals*, 509 U.S. 579, 588, 589 (1993) (quoting Fed. R. Evid. 702). Expert testimony must be evaluated based on the "particular circumstances of the particular case at issue," and may be based on personal experience, so long as the expert "employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 150-152 (1999). Reliability can turn on "identification of a relevant scientific community and an express determination of a particular degree of acceptance within that community." *Daubert*, 509 U.S. at 594 (quotation and citation omitted). Indeed, "in certain fields, experience is the predominant, if not the sole, basis for a great deal of reliable expert testimony." *United States v. Conn*, 297 F.3d 548, 556 (7th Cir. 2002) (*quoting* Advisory Committee Notes, Fed. R. Evid. 702 (2000)). Finally, "background" information is admissible if "reasonably relied upon by experts in the particular field." *Daubert*, 509 U.S. at 595 (quotation omitted).

ARGUMENT

I. DR. FLEMING'S OPINION THAT THE NDA DATA SUBMITTED BY PFIZER WARRANTED A WARNING ABOUT THE INCREASED RISK OF DIABETES IN WOMEN IS RELIABLE AND ADMISSIBLE

Dr. Fleming offers the opinion that, based on the data Pfizer submitted with its original New Drug Application ("NDA"), the Lipitor (atorvastatin) label should have carried a warning about diabetes. *See* Pfizer Ex. 2 at 6. He arrived at this opinion based on his training and experience, his review of the relevant data, and based on the information supplied by other experts. This is precisely the type of review that he provides when consulting for pharmaceutical companies on drug development. It is also the method he used at the FDA when reviewing drug applications and the method used by FDA reviewers today. Pfizer contends that this opinion should be excluded

because Dr. Fleming did not review enough of the NDA and because the opinion is inadequately supported. Neither is true.[3]

A. Dr. Fleming Adequately Reviewed the Relevant Documents to Arrive at His Opinion

Pfizer claims that Dr. Fleming's opinion concerning the NDA data should be excluded because Dr. Fleming did not review enough of the NDA submission to reach his conclusion. "An expert's failure to examine a particular source of information is not grounds for exclusion under *Daubert*, so long as the expert has other 'sufficient facts or data' to support her opinion." *Mathison v. Boston Sci. Corp.*, 2015 U.S. Dist. LEXIS 59047, *54 (S.D. W. Va. May 6, 2015) (quoting Fed. R. Evid. 702 in the context of a plaintiff regulatory expert in the Boston Scientific Corporation transvaginal mesh litigation, MDL No. 2326. Failure to consider particular documents can only be raised as "grounds to cross-examine and impeach [the expert] at trial regarding any perceived oversights in her analysis." *Id*

Here, Dr. Fleming had sufficient facts to support his opinion. Dr. Fleming's opinion concerning the NDA submission is:

> The clinical trial data submitted with the NDA contained reasonable evidence of an association between Lipitor and clinically meaningful increased hyperglycemic abnormalities. Based on these data, Pfizer had a duty to add language to the Warnings section of the Lipitor label to inform prescribers about these abnormalities and to enable physicians to make informed decisions about prescribing the product and monitoring patients for glucose dysregulation and development of diabetes. Moreover, these data triggered an additional obligation on Pfizer's part to undertake additional testing in long-term clinical trials regarding risks of hyperglycemia and new onset diabetes.

Pfizer Ex. 2 at 6.

Dr. Fleming acknowledges that he did not read the entire NDA submission in order to form this opinion, but it was not necessary for him to do so. The information submitted for a New

[3] Pfizer also seeks to exclude a comment Dr. Fleming made at his deposition concerning the NDA and the original Lipitor label. *See* Pfizer Br. at 15-16, *citing* Pfizer Ex. 1 at 126:10-23. Because this is not an opinion Dr. Fleming intends to offer, *see* Pfizer Ex. 2 at 6-7, the Court need not address Pfizer's disagreement with Dr. Fleming's deposition comments.

Drug Application could fill a 20' by 30' room or a semi-truck. *See* Exhibit B at 100:7-101:11. Such a submission is clearly too large for any single person to review in detail. At the FDA, review would be performed by a team. Most of the NDA submission, however, has absolutely no bearing on the limited opinion Dr. Fleming offers about it. Dr. Fleming does not claim to address all aspects of the submission: he does not opine about whether atorvastatin was shown to be sufficiently safe to qualify for approval and he does not opine about the evidence of efficacy in the NDA. These are the topics that the majority of the NDA submission deals with it. Because his *only* opinion pertaining to the NDA concerns the evidence of hyperglycemic abnormalities, it was sufficient for Dr. Fleming to review the portions of the NDA pertaining to those abnormalities. This is especially true because endocrinology and diabetes are Dr. Fleming's specialties and the areas in which he reviewed New Drug Applications at the FDA. Thus, Dr. Fleming is sufficiently familiar with an NDA to find the portion applicable to hyperglycemia and focus his attention there.

Indeed, Pfizer's point appears to be entirely theoretical: it does not identify a single portion of the NDA that it believes would have undermined or affected Dr. Fleming's opinion. Focusing on the selection process alone, Pfizer fails to show that Dr. Fleming missed *any* relevant material in forming this particular opinion. Pfizer's inability to point to a single document that it contends Dr. Fleming ought to have considered is fatal to its claim that Dr. Fleming failed to review enough of the NDA to form his opinion.

Indeed, Pfizer's own regulatory expert, Dr. Rarick, similarly did not review the entire NDA. Like Dr. Fleming, she limited her review to those documents that were relevant to her opinion.

> Q. So you reviewed each of these 3,583 documents?
>
> A. These were the materials in the documents list. I didn't have to review each of them, because as I opened each one of them, I could determine *whether it was relevant to my review*, because you can imagine, when I asked for the entire regulatory record for atorvastatin and FDA communications, I received things that I did not need to review, for example, chemistry, manufacturing controls information that I did not need to look at each page.

(Rarick Dep. at 78:8-78:22, Ex A; emphasis added). By way of example, Dr. Rarick concluded that "Pfizer's submissions and FDA's review and conclusions based on the totality of the scientific evidence have led to appropriate labeling of Lipitor," (Rarick Report at 48, Pfizer Ex. 21), even though she did *not* review adverse event reports to confirm that they were in turn reported to the FDA. She did not believe that was necessary because it was not the focus of her opinion:

> Q. I take it from . . . a previous response . . . that you did not seek as part of your assignment to verify that all pertinent adverse events for this case were submitted to FDA . . .
>
> THE WITNESS: No, that was not -- *adverse event reporting was not my focus at all for this case*. I saw that adverse events were reported in periodic -- you know, certain places in my review, but I was not looking for those or confirming those.

Rarick Dep. at 94:16-95:6, Exhibit A; emphasis added). Nor did she review all of the clinical trials and labeling to compare the Crestor diabetes warning with the Lipitor warning. (*Id.*. at 431:6-431:8).

B. Dr. Fleming's Opinion About the Lipitor NDA Is Properly Supported

1. Dr. Fleming Properly Relies on the Reliable Opinions of Plaintiffs' Other Experts

Pfizer claims that Dr. Fleming's opinion is insufficiently supported because, Pfizer believes, Dr. Fleming is relying entirely on Dr. Jewell's analysis. Pfizer is wrong both as a matter of fact and as a matter of law.

Pfizer claims "Dr. Fleming admitted that he conducted only a superficial review of Dr. Jewell's methodology and could not even recollect what Dr. Jewell did." (Pfizer's Mot. at 2 (citing Fleming Dep. at 99:25-100:9, 107:9-108:23)). The record makes clear, however, that Dr. Fleming *did* review Dr. Jewell's methods:

> Q. Did you look at the methodology behind Dr. Jewell's analysis of the average increase in glucose in the NDA?
>
> A. I in -- at a certain level reviewed his methodology.
>
> Q. What do you think he did?
>
> A. Well, I wouldn't try to recollect *exactly* what he did, but I think his methodology, when I reviewed it, was -- I found that to be sound.
>
> ...

> Q. You agree with what I just said, you should not include the placebos if you're trying to figure out the effect of the drug. Correct?
>
> ...
>
> [A]. Well, I'm confused because I don't recall that that's what Dr. Jewell said.

Pfizer Ex. 1 at 99:25-100:9, 106:23-107:1, 108:4-6 (emphasis supplied). Dr. Fleming went on to answer detailed questions about Dr. Jewell's analysis, and although he did not have perfect recollection of the analysis and was not shown Dr. Jewell's report during this part of the deposition, he explained Dr. Jewell's analysis. *Id.* at 100:10-108:23; 114:20-125:17).[4]

Moreover, there is no doubt that experts are permitted to rely on other experts in forming their opinions. This principle is not only a logical extension of the *Daubert* standard—in which an expert must have sufficient expertise in a particular subject to be qualified to offer an opinion on that subject—but is part of a reliable scientific method, which *Daubert* requires. This is especially true here because reliance on other experts is standard practice at the FDA, where Dr. Fleming worked for 12 years and he routinely relied on summaries by a host of experts, including pharmacology, pharmacokinetics, statistics, etc. *See* Pfizer Ex. 1 at 44:6-19.

Pfizer's argument to the contrary relies on cases that support Plaintiffs' position. For example, rather than holding that one expert may not rely on the opinion of another, *Dura Automotive Systems of Indiana v. CTS, Inc.*, 285 F.3d 609 (7th Cir. 2002) holds precisely the opposite. In *Dura*, the plaintiff submitted a report from a hydrogeologist, Valkenburg, to offer opinions on pollution that depended on mathematical models of groundwater flow. However, Valkenburg lacked expertise in that area; that part of the analysis had been performed by assistants at his firm who had not themselves been designated as experts. *Id.* at 611-12. In ruling on a challenge to Valkenburg's opinion, the trial judge struck the assistants' submissions as untimely, struck Valkenburg's opinion, and granted summary judgment to the defendant.

The Seventh Circuit affirmed solely because it was the untimely disclosure of the experts that Valkenburg relied on that was fatal; the court endorsed the reliance itself as being "common":

[4] Similarly, Dr. Fleming testified that he reviewed, understood, and agreed with Dr. Wells' analysis. Pfizer Ex. 1 at 213:18-213:20.

> [I]t is common in technical fields for an expert to base an opinion in part on what a different expert believes on the basis of expert knowledge not possessed by the first expert; and it is apparent from the wording of Rule 703 that there is no general requirement that the other expert testify as well. . . . But suppose the soundness of the underlying expert judgment is in issue. . . . A theoretical economist, however able, would not be allowed to testify to the findings of an econometric study conducted by another economist if he lacked expertise in econometrics and the study raised questions that only an econometrician could answer. If it were apparent that the study was not cut and dried, the author would have to testify; he could not hide behind the theoretician.

Id. at 613-14. Had the underlying expert submissions (i.e., the assistants' reports) been timely produced and the underlying experts been allowed to testify, Valkenburg could have properly grounded his opinions on those of the assistants; it was only because of the untimely submission that Valkenburg's opinion was precluded: "Without their testimony explaining and justifying the discretionary choices that [the underlying experts] made," the court held, Valkenburg's "testimony would have rested on air." *Id*. at 615. *See also Sommerfield v. City of Chicago*, 254 F.R.D. 317, 326 (N.D. Ill. 2008) (Cole, J.) ("Had Werber testified, the hearsay problem that concerned the court in *TK-7 Corp*. (and in *Dura Automotive*, and *James Wilson*) would not have been present, and the expert testimony would not have been barred. . . . It is only where the assumed version is unsupported that the expert's testimony is objectionable").

Pfizer also cites *In re TMI Litig.*, 193 F.3d 613, 714-16 (3rd Cir. 1999), *amended*, 199 F.3d 158 (3d Cir. 2000), but that decision excluded an expert's opinion because it was not based on a testable hypothesis. That expert was introduced on the subject of exposure assessment, in the context of determining how much radiation residents of Three Mile Island were exposed to. In formulating his opinion, "'he chose to rely blindly upon the conclusions generated by Plaintiffs other experts,' rather than evaluating the 'relative strength or weakness of each of the strands of evidence (e.g., biological dosimetry data) available to him.'" *Id.*at 714 (quoting *In re TMI Litig. Cases Consol. II*, 911 F. Supp. 775 (M.D. Pa. 1996)). The expert could have relied on other experts so long as his own opinion was built on a strong foundation:

> the court finds that Dr. Crawford-Brown's testimony does not by its nature prevent the formation of a testable hypothesis. Rather, Dr. Crawford-Brown *chose to design*

> *his methodology so as not to consist of a testable hypothesis.* Consequently, this factor will weigh against the admission of the proffered testimony.

911 F.Supp. at 825 (emphasis added). According to the court, this was a "key factor" in the *Daubert* analysis: that "the reasoning or methodology underlying the testimony is scientifically valid and of whether that reasoning or methodology." *Daubert*, 113 S.Ct. at 2796. The expert in *TMI* intentionally provided an opinion that was not capable of having its scientific validity tested.

That is not the case here. First, Dr. Fleming's reliance on other experts is both "common" and expected in a complex case like this. Second, he has not provided a scientific opinion that is founded upon defective reasoning or methods, nor has he based his opinion on an underlying opinion with defective methods. He reviewed Dr. Jewell's opinion—which is properly based on scientific and mathematical principles—and, agreeing with Dr. Jewell's analysis, went on to analyze many additional materials to form the basis of his own proper opinion.

Dr. Fleming is entitled to rely on other experts' opinions (in addition to a great deal of information and his own training and experience) when he formulates *his own opinions* about what Pfizer should have done with this information and the adequacy of the Lipitor label. In the *Yaz/Yasmin* MDL, the court reached precisely this conclusion, holding:

> [T]he Court rejects [the defendants]' argument that [Plaintiffs' expert] may not ground any of his opinions on the opinions of others. Rule 702 states that an expert's testimony must be "based on sufficient facts or data." [Plaintiffs' expert] based his testimony on information he obtained from other experts on the issue of increased risk of VTEs posed by YAZ and Yasmin. That is permissible. The Advisory Notes to the 2000 Amendments to Rule 702 make clear that "[t]he term 'data' is intended to encompass the reliable opinions of other experts." Relying on the published works of other professionals is permissible in medicine, as it is in other fields.

In Re: Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Products Liability Litigation, MDL No. 2100, 2011 WL 6302573 (S.D. Ill. Dec. 16, 2011).

A similar situation arose in *Asad v. Continental Airlines, Inc*., 314 F. Supp. 2d 726 (N.D. Ohio 2004) (Wells, J.), where reliance on other experts was challenged but the court allowed the expert opinion. The *Asad* plaintiff offered the testimony of a pediatric neurologist as to the cause of her son's cerebral palsy. She also offered the testimony of a toxicologist, who opined that the

plaintiff had been exposed to toxic levels of CO2 while she was pregnant and that this exposure was a substantial factor in causing the son's cerebral palsy. The defendant claimed that the toxicologist lacked the appropriate expertise to offer an opinion on causation. Rejecting this argument, that court explained:

> While it is true that [the toxicologist] is not independently qualified to exclude the possible causes of Richard Asad's cerebral palsy because he is not board certified in obstetrics and gynecology, pediatrics, pediatric neurology or radiology and does not practice in any of these areas, he properly relied on [the pediatric neurologist's] expert opinion in expressing his own opinion on causation. . . . Rule 703 of the Federal Rules of Evidence specifically allows experts, in reaching their opinions, to rely on "facts outside the record and not personally observed, but of the kind that experts in his or her field reasonably rely on in forming opinions." *Under Rule 703, an expert's testimony may be formulated by the use of the facts, data and conclusions of other experts*. . . .
>
> The causation issue in this case is complex and can only be adequately addressed by a combination of expertise in such fields as pediatric neurology and toxicology. Utilizing [the pediatric neurologist's] opinion and his own expertise in toxicology and occupational injuries, [the toxicologist] is qualified to render an opinion on the cause of Richard Asad's PVL and cerebral palsy. . . .

Id. at 740-41 (emphasis supplied, citations omitted). Because the testimony of the pediatric neurologist was admissible, the testimony of the toxicologist who relied on it was admissible as well. *Id*.

2. The Imbalance Dr. Fleming Identified in the NDA Data Sufficiently Supports His Opinion

Finally, Pfizer claims that Dr. Fleming's opinion about the NDA is unsupported for a wholly different reason. Pfizer claims that Dr. Fleming relies on an imbalance in two of the tables in the Integrated Summary of Safety ("ISS") submitted with the FDA, but that Dr. Fleming himself concedes this is based on an analysis of "a 'very artificial' subgroup" Pfizer Br. at 13. But the actual testimony in context does not contradict or undermine Dr. Fleming's opinion. As Dr. Fleming explained at his deposition, "the point is this is how we pick up adverse event -- or how we start to notice adverse events, by finding them in subgroups where there's greater sensitivity to picking up the signal." Pfizer Ex. 1 at 118:24-119:4. Dr. Fleming explained that, although the subgrouping was artificial, "this is how you approach the evaluation of adverse event reporting for

a drug. . . " *Id.* at 122:17-19. Thus, according to Dr. Fleming, that the subgroup was "artificial" was not unusual and did not render it insignificant or meaningless. Based on Dr. Fleming's experience and expertise, the "artificiality" of the subgroup does not in way undermine Dr. Fleming's opinion based on the analysis of the subgroup and does not reflect a lack of support for that opinion.

II. DR. FLEMING'S OPINION THAT PFIZER SHOULD HAVE INFORMED THE FDA ABOUT THE JAPANESE LABEL CHANGE DOES NOT REQUIRE EXPERTISE IN THE JAPANESE SYSTEM

In 2003, the Japanese regulatory agency required Pfizer to add language to the Lipitor label advising patients with diabetes that their condition could be aggravated, advising all patients that hyperglycemia and diabetes could result from taking Lipitor, and advising that careful observation and regular laboratory tests should be undertaken to monitor for these risks. *See* Pfizer Ex. 2 at 6. Dr. Fleming opines that Pfizer had a duty to inform the FDA about this label change. *Id.* Pfizer contends this opinion should be excluded because Dr. Fleming is not an expert in Japanese drug regulations. This argument should be rejected.[5]

Dr. Fleming's opinion has nothing to do with how the Japanese regulatory authority arrived at the decision to require the diabetes warning. Pfizer Ex. 2 at 6, 28-31. Nor did he need to know whether the Japanese decision had merit; indeed, Dr. Fleming specifically recognized that Pfizer disagreed with it, but Pfizer still had a duty to report to the FDA even if it viewed the decision as "unreasonable or unjustified." *Id.* at 31. Specifically, "[t]he fact that Pfizer did not agree with the Japanese authorities does not excuse it from informing FDA of this label update." *Id.* at 6.

[5] Pfizer also claims that Dr. Fleming said part of the Japanese Lipitor label was "silly." Pfizer Br. at 3, *citing* Pfizer Ex. 1 at 207:25-208:14. But Pfizer fails to mention that Dr. Fleming, also clarified that his use of the word "was not prudent," and that "there could be occasions where [the recommendation at issue] would be appropriate." Pfizer Ex. 1 at 323:14-323:23. But it makes no difference. As noted, FDA regulations do not permit Pfizer or Dr. Fleming to be the judge of whether a foreign regulatory action is proper. They require the manufacturer to report it and to let FDA decide its significance. Indeed, Dr. Fleming's opinion does not turn on the extent to which the Japanese action was appropriate or whether there are particular details Dr. Fleming did not agree with. *See* Pfizer Ex. 2 at 6.

Indeed, the point, and the basis, of Dr. Fleming's opinion is that FDA regulations *require* U.S. drug sponsors to monitor and report such events to FDA. *See* 21 C.F.R. § 314.80; Guidance for Industry (Draft) Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines, March 2001; *see also* Pfizer Ex. 2 at 30-31. This rule requires that manufacturers let FDA be the judge of the significance of a foreign regulatory action. Accordingly, Dr. Flemings opinion calls for expertise in FDA regulations (especially those requiring manufacturers to inform the FDA about foreign regulatory events such as this one), precisely the expertise Dr. Fleming has; expertise in the Japanese regulatory process has nothing to do with the matter.

Other courts have permitted precisely this kind of testimony from experts with expertise in FDA regulations, rather than in foreign regulatory processes. *See In Re: Chantix (Varenicline) Products Liability Litigation*, MDL No. 2092, 2:09-CV-2039-IPJ, slip op., (N.D. Ala. Oct. 3, 2012) (denying motion to exclude evidence or argument concerning foreign regulatory labeling) (Exhibit C); *In Re: Yasmin and Yaz (Drospirenone) Marketing, Sales Practices and Products Liability Litigation*, 2011 WL 6302287 (S.D. Ill. Dec. 16, 2011) (same). This Court should reach the same conclusion.

III. DR. FLEMING'S OPINIONS THAT THE ASCOT TRIAL DID NOT ESTABLISH EFFICACY IN WOMEN AND THE CURRENT LABEL IS MISLEADING ARE ADMISSIBLE

Dr. Fleming offers an opinion concerning the Pfizer clinical trial known as the ASCOT study that breaks down into three opinions, first that the study did not establish efficacy in women for primary prevention; second, that Pfizer's description of ASCOT on the label was misleading; and third, that Pfizer "ignored the clinical and regulatory imperative to identify subpopulations for which the benefit to risk relationship is questionable or not favorable." *See* Pfizer Ex. 2 at 6-7.[6]

[6] Pfizer also seeks to preclude Dr. Fleming from offering statements on the last page of his report as an opinion. *See* Pfizer Br. at 26-28; *see also* Pfizer Ex. 2 at 35. This material, not include in Dr. Fleming's summary of opinions, *see* Pfizer Ex. 2 at 6-7, is not one of the opinions Dr. Fleming seeks to offer.

The first portion of this opinion is the subject of Pfizer's separate motion to exclude testimony that efficacy in women for primary prevention has not been shown. *See* D.E. 970.[7] Plaintiffs respectfully refer the Court to Plaintiffs' opposition to that motion with respect to this branch of Pfizer's motion.

As described in detail in Plaintiffs' Steering Committee Memorandum of Law in Response to Pfizer, Inc.'s Motion to Exclude Expert Testimony and Claims that Lipitor Is Not Effective for and Should Not Be Approved for Primary Prevention in Women ("Ptf. Efficacy Br."), ASCOT was a trial that included some patients who received Lipitor. Pfizer submitted data from the "lipid-lowering-arm" of the study (or ASCOT-LLA) to support an indication for the use of Lipitor in primary prevention (i.e., for people who have not had a cardiovascular injury). The results of ASCOT-LLA were generally understood to support the claim that Lipitor was effective for primary prevention. Plaintiffs' experts, including Dr. Fleming, have opined that ASCOT-LLA did not in fact demonstrate that it was effective for primary prevention in specifically in *women*.

Dr. Fleming has explained in detail the bases for this opinion, including Dr. Wells' analysis, the conclusions of the FDA reviewer regarding this data, and the data from the clinical study report, including three charts referenced in his report that show how the benefit information provided in the label was literally not the full picture. (Fleming Report at 31-35). Dr. Fleming's opinion was focused on the information conveyed in the Lipitor label regarding a particular clinical trial (ASCOT), so the fact that there may be additional evidence that he did not review is not relevant to this specific opinion.

Pfizer claims, however, that Dr. Pfizer claims that Dr. Fleming failed to review additional, later data that could have addressed his concerns about the ASCOT study. *See* Pfizer Br. at 24-25, citing Pfizer Ex. 1 at 227:20-229:9. But whether other trials or other data provide information

[7] Pfizer styles its motion as one to exclude testimony that Lipitor is not effective in women for primary prevention, *see* D.E. 970, but, as noted in Plaintiffs' opposition, Plaintiffs' experts, including Dr. Fleming, opine only that evidence of efficacy is lacking, not that there is evidence for a lack of efficacy.

that was missing in ASCOT would not affect Dr. Fleming's specific opinion about what the ASCOT trial showed. *See* Pfizer Ex. 1 at 227:20-228:3 (explaining that Dr. Fleming is "not offering an opinion" about other data).

Pfizer also claims that Dr. Fleming failed to consider one "particularly important" document. *See* Pfizer Br. at 24. But Dr. Fleming's report shows that he did in fact see the document, referred to and included it in list of sources. *See* Pfizer Ex. 2 at 34 (referencing PFI0040024010, or page 6 of the document at issue); Exhibit B to Fleming Report at 3, 4 (referencing PFI0040024005, or the first page of the document at issue, and PFI004002010).

Pfizer also claims that Dr. Fleming's criticism of the current Lipitor label with respect to diabetes is unsupported by facts, analysis, or methodology. Again, Pfizer misses the point and misunderstands Dr. Fleming's well-founded opinion, which rests on: 1) the body of the report (which discusses, among other things, the regulations and FDA guidance documents that govern drug warnings); 2) the studies and other experts that provide information about the risk of diabetes with Lipitor; 3) a key study that Pfizer used to misrepresent the benefit of Lipitor for women; and 4) Dr. Wells' analysis of that study.

Dr. Fleming's opinion about the current Lipitor label is founded on each of these opinions, and is substantiated by the discussion elsewhere in the report. He summed up his issue with the current label at his deposition: "I believe that it's a watered down version of the description of the risk. And it's ultimately the sponsor's responsibility to take -- to be sure that the label is fully reflective of the data. And in this case, I think Pfizer could have done more to make the label more informative. And this is something they could do irrespective of what FDA has done with this class label." Pfizer Ex. 1 at 302:8-302:17).

IV. DR. FLEMING SHOULD NOT BE PRECLUDED FROM DISCLOSING HIS CONSULTING WORK FOR PFIZER AND OTHER PHARMACEUTICAL COMPANIES

Pfizer also argues that Dr. Fleming should be precluded from discussing information in the Background section of his report and also from mentioning his consulting work with Pfizer. Neither argument has merit.

Rule 26 requires the Plaintiffs to include in their expert reports not only "(i) a complete statement of all opinions the witness will express and the basis and reasons for them," Fed. R. Civ. P. 26(a)(2)(B)(i), but also a statement of "the facts or data considered by the [expert] witness in forming [the opinions]." Fed. R. Civ. P. 26(a)(2)(B)(ii). Dr. Fleming's report fully complies with both requirements: it sets forth his opinions, and it also provides the basis and reasons for those opinions and the facts and data he considered in forming those opinions.

At trial, Plaintiffs certainly do not expect or intend for Dr. Fleming to repeat every item of detail in his report. But the extent to which that evidence can or should be admitted through Dr. Fleming himself, or though other evidence, such as testimony of other witnesses or the admission of the documents cited in the report does not implicate this Court's gate-keeping role under *Daubert*. It is, rather, a matter of this Court's discretion over the presentation of evidence at trial. *See In re Yasmin & YAZ*, 2011 WL 6302287 at *8 (deferring until trial ruling on extent of background and support to which witness could testify); *accord In re DePuy Orthopaedics, Inc. Pinnacle Hip Implant Products Liab. Litig.*, 2014 WL 3557345 *8 (N.D. Tex. July 18, 2014) (same); Fed. R. Evid. 611 (directing court to "exercise reasonable control over the mode and order of examining witnesses and presenting evidence"). This Court should follow the approach taken in *In re Yasmin & YAZ* and *In re DePuy Orthopaedics* and address at trial the nature and extent of summary evidence that Dr. Abramson may properly present in explaining the basis for his opinions.

Nor should Dr. Fleming be precluded from discussing his consulting for Pfizer. That work both explains the methods Dr. Fleming employs when forming regulatory opinions about pharmaceutical products and also shows his *lack* of bias. Indeed, Pfizer takes issue with Plaintiffs'

expert Dr. Abramson for purportedly *not* working with pharmaceutical companies, implying it shows irremedial bias. (Pfizer's Mot. to Exclude Testimony of John Abramson, M.D., at 7). Surely, Dr. Fleming should be able say that he has. More important, Pfizer offers no explanation of how reference to the consulting agreements would harm Pfizer, and although it claims there is a "conflict," it has not explained what, precisely, is the purported conflict. In any event, issues over Dr. Fleming's consulting agreement are not the proper subject of a *Daubert* motion.

CONCLUSION

Dr. Fleming's opinions were formed after a review of the relevant record, using methods similar to the FDA review, and based on proper and reasonable scientific methods. They are therefore proper under *Daubert* and Rules 702 and 703. Pfizer's motion should therefore be denied in its entirety.

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By: /s/ H. Blair Hahn
H. Blair Hahn (Fed. I.D. # 5717)
RICHARDSON PATRICK WESTBROOK
& BRICKMAN, LLC
1037 Chuck Dawley Blvd., Bldg. A
Mount Pleasant, SC 29464
bhahn@rpwb.com
Telephone: (843) 727-6500
Facsimile: (843) 727-6642

Plaintiffs' Lead Counsel

/s/ Jayne Conroy
Jayne Conroy (NY 8611)
David F. Miceli (GA 503900)
SIMMONS HANLY CONROY
One Court Street
Alton, IL 62002
Telephone: (618) 259-2222
Facsimile: (618) 259-2251
jconroy@simmonsfirm.com
dmiceli@simmonsfirm.com

Ramon Rossi Lopez

LOPEZ MCHUGH, LLP
100 Bayview Circle, Suite 5600
Newport Beach, CA 92660
Telephone: (949) 737-1501
Facsimile: (949) 737-1504
rlopez@lopezmchugh.com

Plaintiffs' Executive Committee on behalf the Plaintiffs' Steering Committee